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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/600,272 | 06/20/2003 | Robert G. Komeluk | 07891/003006 | 3330 |

21559 7590 06/17/2004

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

DATE MAILED: 06/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/600,272 | KOMELUK ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/011,356.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/20/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## *DETAILED ACTION*

*Applicant's response filed on 1/12/04 has been acknowledged.*

*Claims1-21 are pending and are examined in this office action.*

*Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is* ***703-872-9306.***

## *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,656,704. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of a substantially pure polypeptide

comprising a sequence selected from the group consisting of SEQ ID NOs: 24, 35, 26, 27, 40 (255-322) and 42 (241-308) of the instant application encompasses the substantially pure polypeptides of SEQ ID NO: 10, 4, 6, 8, 40 and 42 respectively as claimed in the US Pat. No 6,656,704. The SEQ ID NOs: 24, 35, 26, 27, 40 (255-322) and 42 (241-308) of instant applications represent BIR3 domain which corresponds to amino acid sequences of SEQ ID NO: 10 (264-329), 4(265-330), 6(255-322), 8(269-3360, 40(255-322) and 42(241-308) respectively as claimed in the US 6,656,704 patent. Thus the amino acid sequences of SEQ ID NOs: 24, 35, 26, 27, 40 (255-322) and 42 (241-308) and polypeptides comprising these sequences are obvious in view of US 6,656,704.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of Invention:**

The instant invention relates to inhibitor of apoptosis proteins (IAP).

**Breadth of Claims and Guidance Provided in the Specification**

The scope of claims 1-7 encompasses any and all variants (95% identity) of SEQ ID NO: 24, 35, 26, 27, 40 (255-322) and 42 (241-308), wherein the variants are capable of inhibiting apoptosis of a mammalian cell. The scope claims 8-14 encompasses polypeptides that consists of amino acid sequences selected from SEQ ID NO: 24, 35,

26, 27, 40 (255-322) and 42 (241-308), wherein the polypeptide is capable of inhibiting apoptosis of a mammalian cell. The scope of claims 15-21 encompasses a polypeptide that comprises the amino acid sequence selected from SEQ ID NO: 24, 35, 26, 27, 40 (255-322) and 42 (241-308), wherein the polypeptide inhibits apoptosis in a mammalian cell.

At best the specification as filed discloses a polypeptide of SEQ ID NO: 10, 4, 6, 8, 40 and 42 that are capable of inhibiting apoptosis of a mammalian cell (spec pages 27-33). The specification discloses that amino acid sequences of SEQ ID NO: 24, 25, 26, 27, 40 (255-322) and 42 (241-308) represent BIR-3 domain found in SEQ ID NO: 10 (mXIAP), 4(XIAP), 6(HIAP1), 8(HIAP2), 40(mHIAP1) and 42(mHIAP2) respectively (spec. page 23, table-2). However, the specification as filed fails to disclose any polypeptide that consists of amino acid sequences of SEQ ID NO: 24, 35, 26, 27, 40 (255-322) and 42 (241-308) is capable of inhibiting apoptosis of a mammalian cell. Specifically the specification fails to disclose that BIR-3 domain alone or any variant thereof (SEQ ID NO: 24, 35, 26, 27, 40 (255-322) and 42 (241-308)) is capable of inhibiting apoptosis in any kind of mammalian cell. In addition besides the polypeptides of SEQ ID NO: 10 (mXIAP), 4(XIAP), 6(HIAP1), 8(HIAP2), 40(mHIAP1) and 42(mHIAP2), the instant specification fails to disclose any other polypeptide that comprises the BIR3 domain (as claimed) and is capable of inhibiting apoptosis of a mammalian cells.

**State of Art and Predictability**

The inhibitor of apoptosis proteins (IAP) form a highly conserved gene family that prevents cell death in response to a variety of stimuli. All of the *iap* genes isolated from different species have the common structure termed the baculovirus IAP repeat (BIR) that is present in either two or three copies. Another common feature among IAP proteins is a RING finger domain at the C terminus, the function of which still remains unclear. Proteins containing BIR domains have been identified in a wide range of eukaryotic species, including yeast, nematode, insect and several mammalian species including mice, rats, chickens, pigs, and humans. However, membership in the IAP family of proteins requires both the presence of a BIR domain and the ability to suppress

apoptosis. In this regard, many of these BIR-containing proteins are untested with respect to apoptosis suppression. Structure-function studies of IAP family proteins performed to date have uniformly demonstrated a requirement for at least one BIR domain for suppression of apoptosis, although other domains found within some IAPs may also be required under certain circumstances. For example, several of the mammalian, fly, and viral IAPs have a RING domain located near their carboxyl termini. The necessity for the RING domain for suppression of apoptosis appears to depend on cellular context. Taken together, the domain structure of IAPs suggests that the common unit, the BIR domain, can be linked with a variety of other motifs. These non-BIR motifs presumably either diversify the functions of IAPs or provide ways of regulating individual members or subgroups of the family of IAP proteins. Although all IAP family proteins require at least one BIR domain for their anti-apoptotic function, it should be emphasized that not all BIR-containing proteins are necessarily involved in apoptosis regulation as indicated by the failure of the Ac-IAP protein to suppress apoptosis despite harboring a BIR domain. Furthermore, BIR1 and BIR3 domains of XIAP apparently lack caspase-binding capability, despite their striking amino acid similarity to BIR2 (42% for BIR1; 32% for BIR3). Assuming these results cannot be ascribed to trivial explanations such as misfolding of protein fragments taken out of their normal context of the intact protein, these observations suggest that not all BIR domains are created equal. Thus, it is plausible that even BIR domains within the same protein may have distinct functions see Deveraux et al (Gene & Dev. 13(3): 239-252, 1999).

In the instant case variation as claimed also encompasses the conserved motifs like BIR domains, which are considered germane to the biological activity of an IAP polypeptide. Given the broadest reasonable interpretation the scope of invention as claimed encompasses an amino acid sequence which is only 95% identical (5% variation) to the amino acid sequences of SEQ ID NO: 24, 35, 26, 27, 40 (255-322) and 42 (241-308) over the entire length. Such a variation would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere

identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976). Thus considering the scope of invention as claimed it is highly unpredictable that any variant of BIR-3 domain, isolated BIR-3 alone, or any polypeptide comprising only BIR-3 domain (as claimed), would elicits inhibition of apoptosis in any mammalian cell. Therefore considering the scope of invention as claimed and the amount of guidance provided in the instant application, it is unclear how one skill in the art would exercise the invention as claimed without further undue amount of experimentation.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). In instant case screening of any and all natural and non-natural polypeptide containing BIR-3 domain or polypeptide consisting of BIR-3 domain or variants BIR-3-like domains wherein at least 5% of amino acid sequences are added substituted and /or deleted is not considered routine in the art. Making and testing a point mutation is significantly different from the making and testing an amino acid sequences wherein 5% amino acids are added, deleted and/or substituted. The number of possible scenario increase geometrically with increase in percent non-identity. Such making and testing is nothing more than an invitation to further experimentation, since the specification can not be relied on to teach how to make the variants as claimed. One has to engage in extensive making and testing in order to obtain variants that meet the requirements for the claimed inhibition of apoptosis activity. This is not considered routine in the art and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir,1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex

parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed, since applicant has not presented enablement commensurate in scope with the claims.

Claims 1-7 and 15-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The scope of claims 1-7 encompasses any and all variants (95% identity) of SEQ ID NO: 24, 25, 26, 27, 40 (255-322) and 42 (241-308), wherein the variants are capable of inhibiting apoptosis of a mammalian cell. The scope of claims 15-21 encompasses any natural or non-natural polypeptides that comprises the amino acid sequence selected from SEQ ID NO: 24, 25, 26, 27, 40 (255-322) and 42 (241-308), wherein the polypeptides are capable of inhibiting apoptosis in a mammalian cell.

At best the specification as filed discloses polypeptides of SEQ ID NO: SEQ ID NO: 10, 4, 6, 8, 40 and 42 that are capable of inhibiting apoptosis of a mammalian cell. Besides the polypeptides of SEQ ID NO: 10 (mXIAP), 4(XIAP), 6(HIAP1), 8(HIAP2), 40(mHIAP1) and 42(mHIAP2), the instant specification fails to disclose any other polypeptide that comprises the BIR-3 domain (as claimed) is capable of inhibiting apoptosis of a mammalian cells. Similarly the specification fails to disclose any variant of SEQ ID NO: 24, 25, 26, 27, 40 (255-322) and 42 (241-308) that are capable of inhibiting apoptosis of a mammalian cell.

Applicant is referred to the guidelines for ***Written Description Requirement*** published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see http://www.uspto.gov). The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000).

In the instant case besides disclosing the polypeptides of SEQ ID NO: 10 (mXIAP), 4(XIAP), 6(HIAP1), 8(HIAP2), 40(mHIAP1) and 42(mHIAP2), the instant specification fails to disclose any other polypeptide that comprises the BIR-3 domain (as claimed) and are capable of inhibiting apoptosis of a mammalian cells explicitly or implicitly as putatively claimed herein by the applicant (spec page 20, page 23 table-2, pages 27-33).

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406).*

In the instant case the amino acid sequences consisting of variants of SEQ ID NO: 24, 25, 26, 27, 40 (255-322) and 42 (241-308) or polypeptide comprising BIR-3 domains (as claimed) has been defined only by a statement of function that broadly encompasses inhibition of apoptosis in a mammalian cell, which conveyed no distinguishing information about the identity of the claimed polypeptide sequences, such as its relevant structural or physical characteristics. The stat of the art at the time of filing teaches that although all IAP family proteins require at least one BIR domain for their anti-apoptotic function, it should be emphasized that not all BIR-containing proteins are necessarily involved in apoptosis regulation as indicated by the failure of the Ac-IAP

protein to suppress apoptosis despite harboring a BIR domain. Furthermore, BIR1 and BIR3 domains of XIAP apparently lack caspase-binding capability, despite their striking amino acid similarity to BIR2 (42% for BIR1; 32% for BIR3). Assuming these results cannot be ascribed to trivial explanations such as misfolding of protein fragments taken out of their normal context of the intact protein, these observations suggest that not all BIR domains are created equal. Thus, it is plausible that even BIR domains within the same protein may have distinct functions see Deveraux et al (Gene & Dev. 13(3): 239-252, 1999). According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal.
Examiner GAU 1636

SUMESH KAUSHAL
PATENT EXAMINER